Journal of Medical Hypotheses and Ideas (2014) 8, 57–61

Available online at www.sciencedirect.com

Journal of Medical Hypotheses and Ideas

journal homepage: www.elsevier.com/locate/jmhi

REGULAR ARTICLE

Vascular endothelial growth factor blockade: A potential new therapy in the management of cerebral arteriovenous malformations

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Received 30 July 2013; revised 18 October 2013; accepted 19 October 2013
Available online 11 November 2013

KEYWORDS

Arteriovenous malformation;
VEGF;
Bevacizumab;
Obliteration;
Radiosurgery

Abstract Cerebral arteriovenous malformations (AVMs) occur universally in 1.1 per 100,000 people. These malformations are the cause of serious neurological morbidity or even death when they bleed. AVMs are not necessarily static congenital abnormalities. They can undergo internal changes due to angiogenesis resulting in vascular remodelling. They can even regrow after successful therapy. Vascular endothelial growth factors (VEGFs) play an important role in angiogenesis. Drugs that block the action of VEGF on vascular endothelial growth factor receptors (VEGFRs) on the endothelial cell surface are available. This blockade causes an anti-angiogenetic effect. Anti-angiogenic drugs are widely used as adjuvant therapy in the management of cancers because they suppress the formation of new blood vessels required by the tumour for growth. For similar reasons, they are used in the treatment of age-related macular degeneration.

The present treatment options for AVMs are surgery, embolisation and irradiation either on their own or in combination. Irradiation with stereotactic radiosurgery (SRS) offers the advantage of being non-invasive, but it relies on the late radiation effects to achieve its therapeutic goal of complete obliteration. This latent time (1–3 years), during which the risk for a bleed remains, is an inherent drawback of SRS. The histopathology of surgical specimens of post-SRS AVMs demonstrates a role of endothelial cells in repairing the radiation damage. Suppressing their activity post SRS by a VEGF blockade has the potential to enhance the radiation damage and hence speed up the obliteration process and reduce the latent time. It is postulated that such a 'VEGF blockade' could be useful as an adjuvant therapy to SRS. In addition, there is also the potential for a neo-adjuvant use, whereby a VEGF blockade could cause regression in the size of the AVM, making definite therapy easier. The rationale for the VEGF-blockade concept is presented and discussed.

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2251-7294
URL: www.tums.ac.ir/english/
doi:http://dx.doi.org/10.1016/j.jmhi.2013.10.001

Introduction

Arteriovenous malformations (AVMs) have traditionally been considered to be congenital with no postnatal changes during the patient's life. Antenatal diagnosis of the presence of cerebral AVMs is highly uncommon. If fully developed cerebral AVMs were already present at birth, it might be expected that the widespread use of computed tomography (CT) and magnetic resonance (MR) scans in newborns would show an incidence close to that found in adolescence and adults. However this is not the case. The postnatal development of an AVM is a concept supported by clinical observations. Genetic and biological studies have demonstrated that an environmental trigger, the so-called 'second hit', in addition to a genetic predisposition can lead to the development of cerebral vascular lesions [1]. All of the genes associated with vascular malformations of the brain to date have also known or plausible roles in angiogenesis and vascular remodelling [2,3]. An uncontrolled local angiogenesis process, starting after a double hit, could explain the development of AVMs into the entities as seen when they become clinically manifest usually around the age of 4 years or later. This development during childhood and adolescence is a possible explanation as to why this is the period in life when most AVMs are diagnosed, as they rapidly develop together with the growth of the rest of the body [4,5].

During most part of adult life they remain physiologically active and undergo vascular remodelling on the basis of ongoing neo-angiogenesis [6,7]. This can lead to further growth or, more rarely, complete regression [8–16]. Forces that influence this ongoing vascular remodelling are: feeding artery pressures, venous drainage, flow patterns and vascular steal [17,18]. This remodelling is reflected by elevated vascular endothelial growth factor A (VEGF-A) expression in human brain AVMs, [19,20] elevated VEGF plasma levels [21] and active VEGF production by AVM endothelial cells [22]. AVM endothelial cells also significantly overexpress the vascular endothelial growth factor receptors (VEGFRs) 1 and 2, and AVM brain endothelial cells proliferate faster and migrate more quickly [23].

The sprouting of new blood vessels or angiogenesis is a normal physiological process that is most important during embryonic development. This process also happens in adult life during wound healing and during muscle development from exercise and in the formation of collateral vessels to bypass blocked vessels. During malignant tumour development, angiogenesis plays a role in producing extra blood vessels to increase the tumour blood supply [24]. This angiogenetic process is mediated by a signal protein called VEGF. This has actually been found to be a family of factors with the most important one being VEGF-A [25]. Other members are placenta growth factor (PGF), VEGF-B, VEGF-C and VEGF-D. These members of the VEGF family bind to VEGFRs on the cell surface, whereby they activate intracellular pathways. Two such receptors have been identified, namely VEGFR-1 and VEGFR-2, of which VEGFR-2 seems to mediate almost all of the signalling [24,25].

Present treatment options for AVMs are: (a) surgery for those lesions that are resectable and (b) radiation therapy under the form of stereotactic radiosurgery (SRS) for those lesions that are irresectable or when the patient refuses surgery. Embolisation is helpful in making the surgery easier but is not always successful on its own [26,27].

SRS, by gamma knife and linear accelerator- or cyclotron-produced charged particles, is a well-established treatment option [28]. However, lesions most effectively treated have volumes < 15 cc or a maximum diameter of ± 3 cm. As the AVM volume increases, it becomes more and more difficult to obtain an optimal balance between successful obliteration and radiosurgical complications [29]. Even when radiosurgery can be given with a small risk of side effects, there is always a latent period (1–3 years) between the irradiation procedure and the eventual obliteration. During this time the patient remains at risk for a bleed, and only when the AVM is completely obliterated can the patient be considered cured [28].

The pathophysiological events after radiosurgery have been well documented in surgical specimens post radiosurgery and consist initially of endothelial cell death and denudation of the vessel wall surface followed by a reactive subsequent increased endothelial cell proliferation in an attempt to repair the denudation of the vessel wall [30]. The remaining areas of denudation then trigger a thickening of the intima layer by proliferation of smooth muscle cells [31]. These changes in turn lead to thrombosis of the AVM vessels. If this process is sufficiently extensive it leads to complete obliteration [32,33].

The hypothesis

Current traditional methods for treating brain AVMs are based on the concept that they are congenital and do not undergo change during the patient's life. However that is not necessarily the case and there is evidence that AVMs are dynamic entities undergoing vascular remodelling driven by angiogenesis. The process of angiogenesis is well understood and is stimulated by activating cellular membrane receptors. Monoclonal antibodies that block these interactions have been developed for oncological use. They block the tumour-induced angiogenesis needed for tumour growth and are routinely used in the treatment of certain cancers.

A similar VEGF blockade has potential in the management of AVMs by suppressing the ongoing angiogenesis, a process that is responsible not only to maintain the AVM but also to repair the radiation-induced damage. Such a VEGF blockade could be used as adjuvant therapy following the irradiation procedure to suppress the repair process by proliferating endothelial cells and therefore speed up the thrombotic process responsible for obliteration. This would reduce the latent period and the time at risk for a new bleed, and in turn would have significant clinical and health economic implications. A neo-adjuvant use would be aimed at suppressing the ongoing vascular remodelling and reducing the vascular density and to possibly make the AVM smaller and more manageable for surgical or radiosurgical interventions.

Evaluation of the hypothesis

Drug-based anti-angiogenesis therapy is well established in oncology [34,35].

Tumours are dependent on new blood vessel formation for their growth and they actively promote angiogenesis by releasing VEGFs in their immediate environment to achieve this. A treatment strategy to interfere with this angiogenesis has long been seen as a way to help in the eradication of tumours. A variety of drugs exist that have proven anti-angiogenesis

effects and these can basically be divided into drugs specifically developed for their primary anti-angiogenetic effect, monoclonal antibodies, and drugs with secondary anti-angiogenetic effect in addition to their primary therapeutic use. The monoclonal category has been used extensively in oncology and their therapeutic action as well as side-effect profile are well established. A number of drugs with a secondary anti-angiogenic effect are also in clinical use with a well-established therapeutic and side-effect profile [36–38].

One of the most commonly used anti-angiogenesis agents in oncology is bevacizumab (Avastin®), a monoclonal antibody that binds to VEGF-A, rendering VEGF-A ineffective in its stimulation function of the cell membrane receptor. There is extensive clinical experience for a variety of cancers with this drug. Bevacizumab is Food and Drug Administration (FDA)-approved for the treatment of: (a) metastatic colorectal cancer, (b) non-small cell lung cancer, (c) glioblastoma and (d) metastatic renal cell carcinoma.

In addition, it is used in ophthalmology for age-related macular degeneration [39].

The proliferative activity of endothelial cells in AVMs is also governed by angiogenesis factors acting on their cell membrane receptors, and blocking this interaction with anti-angiogenesis drugs should therefore have therapeutic potential in the management of AVMs. This could be called a VEGF blockade [40]. If the post-radiation increased endothelial cell proliferation in reaction to the radiation damage could be blocked, then larger areas of denudation would remain. This would in turn be a more extensive trigger for thrombosis in the AVM vessels.

The concept of attempting to improve the therapeutic benefit from radiosurgery is not new [41]. Sims and Plowman [42] tried this by protecting the normal surrounding brain from the radiation effects. Their radiosurgical treatment of large AVMs explored the use of gamma linolenic acid (GLA), which has a protective effect on normal brain. They found that GLA did not improve the therapeutic ratio as it also offered protection for the AVM against the effect of the radiation.

Adjuvant use post radiosurgery

Bevacizumab only has a suppressive effect on angiogenesis, which is lost once the drug is stopped as seen in tumour angiogenesis suppression. Therefore, a continuous blockade starting soon after radiosurgery and achieved by regular administration of bevacizumab 10 mg kg^{-1} intravenous infusion (IVI) every 2 weeks would be required until obliteration is complete [35]. This is also the way bevacizumab is used in oncology, whereby angiogenesis is blocked for many months/years [43–45]. The side-effect profile of such long-term administration is well established. Most common adverse effects are: (a) hypertension, (b) gastrointestinal perforation, (c) wound-healing complications (traumatic and surgical) and (d) haemorrhage in the form of haemoptysis, gastrointestinal bleeding, central nervous system (CNS) haemorrhage and vaginal bleeding [34,35].

The safety and effectiveness of bevacizumab have not been established in paediatric oncology patients [35]. Because long-term use of a VEGF blockade could hamper final development of organs in the body of patients who are still growing, its use in children and adolescents should only be considered once sufficient clinical data from adult studies have been obtained.

The possible outcomes of such an intervention could be to: (a) speed up the obliteration process and hence reduce the period at risk for bleeding, (b) improve the overall obliteration rate for radiosurgery, (c) achieve the same obliteration rate with lower radiation doses and (d) a combination of these factors.

The effect of bevacizumab on AVMs has been demonstrated in an animal model. Walker et al. [46] showed that VEGF antagonism by bevacizumab reduced the vessel density in AVMs in the adult mouse brain.

Bevacizumab has also been shown to have radiation-sensitising properties when used in combination with radiation [47]. Although this is desirable in terms of the radiation effects on the AVM itself, there is an as-yet not-quantified and unknown risk of increased damage to normal blood vessels in the vicinity of the AVM if these would be exposed to low doses of radiation in combination with bevacizumab. Hence at this stage the safest use would be post radiosurgery [48].

Monitoring the effect of a VEGF blockade after radiosurgery would be essentially the same as after radiosurgery alone, whereby regular radiological imaging is done to observe how quickly and when the complete obliteration has occurred. Although VEGF plasma levels can be measured in patients and are significantly elevated in untreated AVM patients compared to normal individuals [21], their role in monitoring the VEGF blockade would have to be investigated.

Neo-adjuvant use

A VEGF blockade could have therapeutic implications in the sense that it could possibly shrink the size of the AVM making neurosurgical removal easier. A reduction in size would also make SRS safer, because the risk of developing symptomatic radiation injury after radiosurgery is related to lesion diameter and volume.

The influence on the symptoms due to the AVM's presence such as headaches and epilepsy is speculative, but the possibility exists that these might be alleviated by a VEGF blockade.

Discussion

Radiosurgery is a frequently used treatment option. A meta-analysis in 2011 by van Beijum et al. [49] looking at a total population of 13,698 patients diagnosed with an intracranial AVM, found that 9436 (69%) of the patients were managed by radiosurgery. The post-radiosurgery intracranial haemorrhage rate for this group was 1.7 per 100 person years. Other studies have reported post-radiosurgery annual haemorrhage risks ranging from 1.14% to 2.2%, [50–53] and an overall permanent morbidity of a re-haemorrhage from 30% to 40% with a mortality rate between 9% and 12.5% [54,55]. If indeed the post-radiosurgery VEGF blockade reduces the latent time and hence shortens the period at risk for a haemorrhage, this would have significant clinical and health economic implications.

Radiosurgical AVM obliteration is dose dependent with higher doses giving an earlier and higher obliteration rate. Unfortunately higher doses also mean higher complication rates, and hence any radiation dose reduction that would be possible without negatively affecting the obliteration rate would improve the therapeutic ratio.

If an adjuvant VGEF blockade would indeed show therapeutic effect it would subsequently become possible to investigate lowering the radiation dose and still achieve the same obliteration rate. It would also open the way for a neo-adjuvant use to facilitate the use of surgery or SRS.

Conclusion

Based on the concept that AVMs are dynamic entities with ongoing vascular remodelling driven by angiogenesis, and the fact that repair of radiation damage is also related to angiogenesis, the use of anti-angiogenic drugs has theoretical therapeutic potential in the overall management of this disease and this should be studied in clinical trials.

Conflict of interest

None declared.

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